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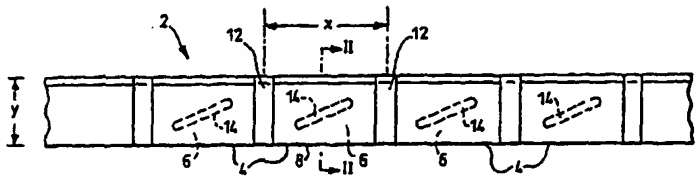

(57) Abstract

A string (2) of pouches (4), each having a tag (14) contained therewithin, is made from a microfilamentous polypropylene fabric which is post-irradiation grafted with a monomer or monomers. The monomer or monomers includes functional groups arranged to be covalently bonded to other compounds or moieties. A method using the string for preparing a library of compounds in a combinatorial technique is also described.

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SOLID SUPPORT MATERIALS

This invention relates to solid support materials, methods of using and/or manufacturing same and apparatus therefor. Particulary, although not exclusively, the invention relates to solid support materials for the purposes of solid phase synthesis and for supporting another material, compound or moiety which may be used for solid phase synthesis or solution phase synthesis.

It is well-known to use solid support materials in solid phase chemical and biochemical syntheses, immunoassays and hybridization reactions and for supporting reagents, for example catalysts or enzymes and there have been numerous prior publications of proposed materials and processes for preparing the same. Selected prior disclosures are described further below.

WO96/16078 (Pfizer) describes the use of paper which has been treated to enable reagents to bind thereto. For example, if the reagents are amino acids or peptide fragments, the paper may carry anchor groups to releasably bind the carboxylic acid groups of amino acids to the paper. The document also describes the use of a laminate comprising a solid material, for example cross-linked polystyrene resin containing amino groups, sandwiched between fibrous sheets, for example non-woven polypropylene sheets.

WO90/02749 (Forskningscenter Riso) describes a solid support for use in peptide synthesis which comprises a thin polyethylene sheet or film which has been grafted with polystyrene chains in a radical-initiated process in which the polyethylene sheet or film is immersed in a solution of optionally-substituted styrene monomer in an

alcohol and subjected to gamma radiation. Such a grafting process wherein the material to be grafted is irradiated in the presence of monomer is described as a "mutual" grafting process.

WO91/04266 (Loseko) describes the preparation of a solid surface for peptide synthesis by a mutual grafting process using acrylic acid solution as a monomer.

WO98/31732 (Irori) describes a method of radiation grafting to polymeric surfaces which addresses the problem of providing graft polymers of sufficiently high levels of grafting such that the resulting grafted polymer is suitable for use as a support in synthesis and screening, particularly for use in combinatorial synthetic and high-throughput screening protocols. The solution to the problem, in one embodiment, comprises using an acid, for example sulphuric or nitric acid, to chemically abrade the surface prior to grafting in a mutual grafting process. In another embodiment, the problem is stated to be solved by physically abrading the polymer to be grafted prior to the grafting.

One problem with the mutual technique that has been appreciated by the present inventors is that it is difficult to control the length of the grafted chains, since there is a tendency for the monomer to self-polymerize; and, it is difficult to control the density of chains attached to the grafted polymer. As a result, it may be difficult to maximise the number of sites to which moieties to be supported can be bound and, furthermore, if the grafted chains are long, they may become tangled, thereby reducing their availability for supporting moieties. Another problem with the mutual technique is that it is difficult to heat the grafted material (for

example in powder form) to shape or re-shape it, because the relatively long grafted chains increase the melt flow index of the molten material, rendering re-shaping of the grafted material difficult to predict and control.

In general terms, solid support materials for use in synthesis and screening techniques suitably have one or more of the following properties:

(a) they are not brittle, but are flexible, suitably so that they can be made into sheets;

(b) they are inert to the solvents and/or reagents that may be used in downstream synthetic or screening processes;

(c) they are thermoplastic and can be extruded or otherwise treated to enable desired shapes to be made;

(d) they have a relatively large number of sites to which moieties to be supported can be bound and, therefore, the amount of material that can be supported is relatively high per unit mass or per unit area;

(e) they have a high surface area for supporting materials;

(f) they are thermally stable, so they do not melt, deform or become brittle on heating.

Various methods of making a library of compounds on solid supports and/or of providing means for uniquely identifying and tracking the solid supports during a sequence of process steps have been proposed. Selected prior disclosures are described further below.

WO96/16078 (Pfizer) describes a method of making a library of compounds using a three-dimensional stack of

individual sheets on each of which reaction zones are defined. The stack of sheets is cut into strips which are subjected to different reactions. Disadvantageously, once the stack has been cut into strips, much of the order initially present in the stack is lost, there making the tracking of the processes to which individual reaction zones are subjected difficult, since the identity of each reaction zone and the processes to which it is subjected must be recorded at each stage.

WO98/15825 (Irori) describes a "Directed Sorting" approach to solid phase combinatorial chemistry which uses matrix with memory microreactors. In the approach, each microreactor is assigned to one specific compound and the microreactors are pooled in appropriate reaction vessels. After appropriate reactions, and/or washing, each microreactor is individually identified and then directed to the next reaction vessel. It will be appreciated that this approach disadvantageously requires a very large number of identifications of the microreactors in the course of preparing a library of compounds.

It is an object of preferred embodiments of the present invention to address some of the above described problems.

According to a first aspect of the invention, there is provided a method of supporting a compound or other moiety, the method using a fabric which comprises a plastics material.

Said fabric may comprise filaments having a diameter of at least 5μm, preferably at least 10 μm, more preferably at least 15 μm. Said filaments may have a diameter of 500 μm or less, suitably of 200 μm or less,

preferably 100 μm or less, more preferably 60 μm or less, preferably 30 μm or less.

Said fabric may have a density of at least 20 g/m^2, suitably at least 40 g/m^2, preferably at least 60 g/m^2, more preferably at least 80 g/m^2. Said density may be less than 250 g/m^2, suitably less than 200 g/m^2, preferably less than 150 g/m^2, more preferably 120 g/m^2 or less.

Said fabric is preferably laminar. It may have a thickness as described hereinafter.

Said fabric may be woven or non-woven. It is preferably non-woven.

Said fabric (especially a non-woven fabric) may comprise an array, preferably a random array, of microfilaments which are, suitably, heat-welded in position. A structure which is relatively open (and which therefore can be readily penetrated by liquids used in downstream process steps) may be formed. The microfilaments are suitably not embedded in or otherwise associated with a binder material. Said fabric preferably comprises thermally bonded endless filaments.

Said fabric is preferably thermoplastic.

Said fabric preferably includes a first polymeric material which may have any feature of the first polymeric material described hereafter. Said first polymeric material may be a graft polymer. Such a graft polymer may be prepared by any technique. Said graft polymer is preferably prepared using one or more monomers which may have any feature of the one or more monomers described hereafter. Preferably, said graft polymer is prepared by

an irradiation grafting technique, which may be a mutual irradiation technique. More preferably, it is prepared as described according to the seventh aspect discussed hereafter.

Preferably, said fabric does not include a functional group which is able to form a hydrogen bond, for example with another functional group of the same type.

Said fabric preferably has reactive sites via which said compounds or other moieties may be bonded to the fabric. Said reactive sites preferably allow said compounds or moieties to be covalently bonded to the fabric. Preferably, said reactive sites do not include moieties involved in hydrogen bonding within said fabric. Preferably, said reactive sites are not hydroxy groups. Preferably, the physical strength of said fabric is not reduced to an appreciable extent by the bonding of said compounds or other moieties to said reactive sites.

Said fabric preferably includes a linker moiety which is suitably arranged to allow other compounds or moieties to be covalently bonded thereto and/or cleaved therefrom when required. Said linker moiety may be as described in any statement herein.

The method preferably includes the step of forming a covalent bond between said compound or other moiety and said fabric. Preferably, an intermediate moiety is arranged between said fabric and said compound or moiety which is supported and, suitably, said compound or other moiety is covalently bonded to said intermediate moiety. Said intermediate moiety is preferably covalently bonded

to said fabric. Said intermediate moiety may include a linker moiety as described in any statement herein.

Preferably, said fabric makes up more than 70 wt%, suitably more than 80 wt%, preferably more than 90 wt%, more preferably more than 95 wt% of a solid support material used in said method for supporting a compound or other moiety. Preferably, a said solid support material for use in said method consists essentially of said fabric.

According to a second aspect of the invention, there is provided the use of a fabric, especially a non-woven fabric, as a solid support for supporting a compound or other moiety.

According to a third aspect of the invention, there is provided a solid support for supporting a compound or other moiety, said solid support comprising a fabric, especially a non-woven fabric.

Said solid support preferably includes a linker moiety as described herein which is arranged to allow said compound or other moiety to be covalently bonded to the support and/or cleaved therefrom when required.

Said solid support preferably defines a plurality of distinct regions for supporting different compounds or moieties.

Said fabric may include an associated identification means. Said identification means is preferably arranged to allow one part (suitably a part which may support a first compound) of said fabric to be distinguished from another part (suitably a part which may support a second

compound different to said first compound). Said identification means may comprise, for example, numbers, letters, symbols, colours in a coded combination, Smiles strings, bar-codes, chemical structures, marked or printed punched card formats and ultraviolet-readable devices, such as magnetic strips. Preferably, said identification means comprises an electro-magnetically readable device, for example a device arranged to be read by a Rf transmitter or a magnetic readable device. Said identification means preferably includes an encoded identifier arranged to be read by a reader. The encoded identifier preferably includes a unique code. The identity of the encoded identifier and/or information associated with said identification means is preferably predetermined and is preferably not changeable after the identification means has been associated with said fabric. For example, said identification means is preferably not re-programmable and/or otherwise arranged to receive new data after it has been associated with said fabric.

According to a fourth aspect of the invention, there is provided a solid support for supporting a compound or other moiety, the support being flexible and including means (hereinafter "enclosure means") defining an enclosed region.

Said enclosure means preferably comprises two layers of material which is preferably laminar material. Said laminar material is preferably porous. Said laminar material may have a thickness of at least 100 μm, suitably at least 200 μm, preferably at least 300 μm, more preferably at least 400 μm, especially at least 500 μm. The thickness may be less than 5000 μm, preferably less than 4000 μm, more preferably less than 2000 μm, especially less than 1000 μm. Said two layers are

preferably attached to one another along at least part of their extent to define at least part of a boundary of said enclosed region. Said laminar material may comprise a woven or non-woven fabric as described in any statement herein. It preferably comprises a non-woven fabric.

Said enclosed region preferably has a variable volume and/or a variable three-dimensional shape. Said enclosed region preferably has a substantially quadrilateral, more preferably a substantially rectangular shape in plan view. The width of said enclosed region (in plan view) may be at least 5 mm, preferably at least 10 mm, more preferably at least about 15 mm. The width may be less than 100 mm, preferably less than 50 mm, more preferably less than 40 mm, especially less than 30 mm. The length of said enclosed region (in plan view) may be at least 5 mm, suitably at least 10 mm, preferably at least 15 mm, more preferably at least 20 mm, especially at least 25 mm. The length may be less than 100 mm, suitably less than 80 mm, preferably less than 60 mm, more preferably less than 50 mm, especially less than 40 mm.

It will be appreciated that, for a given loading of non-woven or woven material, variation of the physical size of each enclosure means will lead to an increase or decrease in the amount of product supported by each support in subsequent process steps.

Where said enclosed region is quadrilateral in shape, at least one of the sides (hereinafter "said first side") of the quadrilateral may be defined by a fold in the material, suitably said laminar material, from which the solid support is made. Preferably, a side of the quadrilateral opposite said first side (hereinafter "said opposite side") is defined by physically attaching two

layers of material together. This may suitably be accomplished by welding, for example, heat welding, said two layers together so that the line of the heat weld defines a boundary of said enclosed region. Heat welding may be accomplished using direct heat or by using an alternative energy form (for example ultrasonic means) that generates heat in materials to be joined together. Said first and second sides are preferably elongate sides of said enclosure means. Transversely extending boundaries of said enclosure means may be defined by physically attaching said two layers of material together, for example by heat welding.

Said enclosure means is preferably substantially fully enclosed. It preferably does not having any gaps which are smaller than the physical size of anything (e.g. resin beads of 100-200 mesh) that may be contained therewithin. Preferably, said enclosure means does not include any gaps having any dimension greater than 1 mm, more preferably none greater than 0.5 mm, especially none greater than 0.25 mm.

Said enclosed region preferably retains, for example entraps, an entrapped member or material. An entrapped material could be a resin (or the like), for example resin beads, which itself may be arranged to support a compound or other moiety. Preferably, however, said enclosed region retains an identification means as hereindescribed. Such an identification means may suitably have no dimension greater than 30 mm, preferably none greater than 20 mm. No dimension may suitably be less than 1 mm. Preferred identification means are elongate.

Said support preferably includes a plurality of enclosure means defining a plurality of enclosed regions,

each being as described herein and each preferably being substantially identical, except for the identity of a code associated with an identification means (if provided). Preferably, adjacent enclosure means of said support have common transversely extending boundaries which define parts of adjacent enclosure means. Said support may comprise an elongate string, suitably having at least 10, preferably at least 100, more preferably at least 500, especially at least 1000 enclosed regions, preferably in line with one another and contiguous. Preferably, said enclosed regions are arranged to be disconnected from one another. Thus, said support may be divided, for example cut, between adjacent enclosed regions. Said enclosure means is preferably arranged such that such a division does not significantly affect the integrity of the enclosed region.

Said support is preferably non-self-supporting. It may be sufficiently flexible as to allow it to be formed into a roll.

According to a fifth aspect of the invention, there is provided a method of manufacturing a solid support according to the fourth aspect, the method comprising causing a flexible material to define said enclosed region.

Said flexible material is preferably initially in the form of an elongate strip which preferably comprises a single layer of material, preferably a said fabric as described herein. The method preferably includes the step of folding the elongate strip, suitably about a fold line extending substantially parallel to the elongate extent of the strip and preferably extending centrally along the elongate extent, suitably so that the strip is folded

along its middle. Preferably, the strip is only folded along a part of its extent. Preferably, it is folded from a point extending from a free end thereof. After folding, the strip is preferably arranged with the fold line below the other parts of the strip so that an upwardly open receptacle is defined.

The method preferably includes securing opposite parts of the folded strip together. Preferably, initially, opposing transversely extending parts are secured together, preferably by heat welding.

The method preferably includes the step of associating another member, for example an identification means, with said enclosed region. More preferably, the method comprises positioning an identification means within the folded strip described above. The method subsequently preferably comprises arranging the strip so that said identification means is enclosed in said enclosed region. The method may comprise securing the remaining opposing parts of the folded strip together. The method may comprise securing together opposing parts, suitably arranged adjacent free edges of the strip, which are spaced from and extend substantially parallel to said fold line. The method may comprise securing together opposing parts which are spaced from said aforementioned opposing transversely extending parts and which preferably extend substantially parallel thereto.

In the method, a continuous strip comprising a string of enclosed regions may be manufactured. To this end, after the enclosed region described above has been made, an enclosed region adjacent said enclosed region (hereinafter "said first enclosed region") may be made by securing together opposing parts of a folded region of the

strip upstream of said first enclosed region, suitably with an identification means therebetween.

According to a sixth aspect of the invention, there is provided apparatus for use in a method according to said fifth aspect, the apparatus comprising:

feeding means for feeding an elongate strip of material;

folding means for folding the elongate strip; and

securing means for securing parts of the strip together to define an enclosed region.

Said feeding means preferably feeds the strip towards the folding means. Said securing means is preferably arranged to heat weld said parts together to define said enclosed region.

Said apparatus preferably includes delivery means for delivery of another member, for example said identification means, towards the elongate strip for enclosure in said enclosed region, before said securing means secures parts of the strip together.

Said apparatus preferably includes reading means for reading the identity of said identification means, with information relating to said identity suitably being electronically recorded. Where said support includes a multiplicity of enclosed regions (as is preferred) each identification means is preferably read and its identity recorded so that the order of the identification means along the support is recorded.

According to a seventh aspect of the present invention, there is provided a method of making a solid support for use in synthesis or screening, for example for supporting a compound or other moiety, the method comprising irradiating a first polymeric material and subsequently contacting it with one or more monomers in order to prepare a graft polymer.

Said solid support may be for use in solid phase chemical and biochemical syntheses, immunoassays, hybridization reactions or for supporting reagents and scavengers. Preferably, said support is used in synthesis, for example in chemical synthesis or as a reagent support. More preferably, said support is used in synthesis, especially in combinatorial chemistry.

Unless otherwise stated in this specification, where any group is stated to be optionally-substituted, optional substituents may be selected from halogen (preferably fluorine, chlorine or bromine, especially chlorine) atoms and alkyl, acyl, nitro, cyano, alkoxy, alkoxyalkyl, hydroxy, amino, alkylamino, sulphinyl, alkylsulphinyl, sulphonyl, alkylsulphonyl, sulphonate, amido, alkylamido, alkoxycarbonyl, halocarbonyl (especially chlorocarbonyl, haloalkoxy,) and haloalkyl (especially chloroalkyl), groups.

Unless otherwise stated in this specification, an alkyl group may have up to 12, suitably up to 10, preferably up to 8, more preferably up to 6, especially up to 4 carbon atoms, with methyl and ethyl groups being preferred.

Unless otherwise stated, preferred aryl, cycloalkyl, cycloheteroalkyl and heteroaryl, groups have six ring atoms.

Said first polymeric material is preferably a thermoplastic polymer. It may be a copolymer. Said first polymeric material may have a melt flow index (MFI), measured according to ASTM D1238, in gram/10 minutes, of at least 0.5, suitably at least 2, preferably at least 5, more preferably at least 10. Said MFI may be less than 50, suitably less than 40, preferably less than 30, more preferably less than 20, especially 15 or less.

Said first polymeric material is preferably hydrophobic. Said first polymeric material is preferably thermoplastic.

Said first polymeric material may be any material that can be grafted in the method described. Said material may comprise an optionally-substituted polyolefin, silicone polymer, natural or synthetic rubber, polyurethane, polyamide, polyester, formaldehyde resin, polycarbonate, polyoxymethylene, polyether, epoxy resin or a co-polymer comprising any of the aforesaid.

Optionally-substituted polyolefins may be selected from polyethylene; polypropylene; polyisobutylene; acrylic polymers, such as polyacrylate, polymethacrylate, polyethylacrylate; vinyl halide polymers, such as polyvinyl chloride; fluoropolymers such as polytetrafluoroethylene, chlorotrifluoroethylene and fluorinated ethylene-propylene; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride;

polyacrylonitrile; polyvinylketones; polyvinyl aromatics; and polyvinyl esters, such as polyvinylacetate.

Suitably, optionally-substituted polyolefins are selected from polyethylene, polypropylene, partially or fully fluorinated polyolefins and co-polymers including any of the aforesaid. Preferably, optionally-substituted polyolefins are selected from polyethylene, polypropylene and partially or fully fluorinated polyethylene or polypropylene. More preferably, said optionally-substituted polyolefins are polyethylene and polypropylene polymers, with unsubstituted polyethylene and polypropylene being especially preferred. Unsubstituted polypropylene is most preferred.

Optionally-substituted silicone polymers include polydimethylsiloxane.

Natural or synthetic rubbers include butadiene-styrene copolymers, poly-isoprene, polybutadiene, butadiene-acrylonitrile copolymers, polychloroprene rubbers, polyisobutylene rubber, ethylene-propylenediene rubbers, isobutylene-isoprene copolymers and polyurethane rubbers.

Preferred polyamides are Nylon 66 and polycaprolactam.

A preferred polyester is polyethylene terephthalate.

Said first polymeric material is preferably isotactic.

Said first polymeric material is preferably substantially insoluble in water at 25°C. The first

polymeric material is generally less soluble in organic solvents, for example dichloromethane, than a polymer made from said one or more monomers. The graft polymer suitably has the low solubility of the first polymeric material, together with the attached chemistry of the one or more monomers.

Said first polymeric material is preferably selected from an optionally-substituted polyolefin, polyamide, polyurethane, polyester or a copolymer of ethylenically-unsaturated comonomers, for example of an olefin and vinyl acetate. More preferably, said first polymeric material is an optionally-substituted polyolefin, as described above.

A first monomer for use in said method is preferably unsaturated and is, more preferably, ethylenically-unsaturated. Said monomer preferably includes a functional group capable of undergoing a reaction, suitably an electrophilic or nucleophilic reaction, for example a substitution reaction. This suitably enables other groups or moieties to be reacted with a moiety derived from said monomer(s) after the graft polymer has been prepared in said method. Said monomer may include a functional group selected from optionally-substituted aryl and heteroaryl groups, carboxylic acid, carboxylic acid derivatives, amines, amine derivatives, inorganic acid, sulphate, hydroxy and substituted alkyl, cycloalkyl and cycloheteroalkyl groups and protected versions of any of the aforesaid.

Protected versions of the functional groups will be well-known to skilled persons in the art. Details of protecting groups may be found in Protective Groups in Organic Synthesis, Theodora Green and Peter Wuts (1991)

John Wiley & Sons, Inc, the contents of which are incorporated herein by reference.

A preferred aryl group is phenyl. A preferred heteroaryl group is pyridyl. Preferred carboxylic acid derivatives include ester, amide (including cyclic amides such as pyrrolidine moieties) and acid halide groups. Amides are especially preferred carboxylic acid derivatives. Preferred functional groups based on inorganic acids include sulphur-oxo acid groups, especially a sulphonic acid group, and phosphorus-oxo acid groups, especially a phosphoric acid or a phosphonic acid group. Preferred alkyl groups are C_{1-6}, more preferably C_{1-4}, especially C_{1-2} alkyl groups. A preferred cycloalkyl group is cyclohexyl. A preferred cycloheteroalkyl group has five or six ring atoms and includes an oxygen or nitrogen ring atom.

Optional substituents of aryl or heteroaryl groups are preferably capable of being reacted in a substitution reaction, for example a nucleophilic or electrophilic substitution reaction. Said optional substitutents may be optionally-substituted alkyl groups. Preferably, said optional substituents are optionally-substituted haloalkyl groups. More preferably, said optional substituents are haloalkyl groups, with mono-halogenated groups being preferred. A chlorine atom is a preferred halogen atom of a said haloalkyl group. Preferred haloalkyl groups have 1-4, especially 1-2 carbon atoms. A chloromethyl group is an especially preferred haloalkyl group.

Substituted alkyl, cycloalkyl and cycloheteroalkyl groups preferably include a substituent capable of being reacted in a substitution reaction, for example a nucleophilic or electrophilic substitution reaction. Said

substituent preferably includes a halogen atom, especially a chlorine atom. Preferred alkyl, cycloalkyl and cycloheteroalkyl groups are monohalogenated.

Preferred functional groups of said monomer include carboxylic acid, carboxylic acid derivatives, optionally-substituted phenyl and organic basic groups based on pyrrolidine or pyridine. Preferred functional groups are polar.

Said functional group of said first monomer may be linked to the C=C moiety of the monomer by any suitable means. Preferably, said functional group is a vinyl or allyl group. A vinyl group is most preferred.

Preferably, said first monomer is selected from the group consisting of an ethylenically-unsaturated carboxylic acid, for example acrylic acid or an alkyl-substituted ethylenically-unsaturated acid, for example methacrylic acid; an ethylenically-unsaturated carboxylic acid amide, for example acrylamide; an ethylenically-unsaturated carboxylic acid amine, for example an alkylamine acrylate such as butylamine acrylate; an ethylenically-unsaturated organic base, for example vinyl pyrrolidine or vinyl pyridine; and an ethylenically-unsaturated optionally-substituted phenyl compound, for example styrene or a substituted styrene.

Preferably, said first monomer is selected from a said ethylenically-unsaturated acid; a said ethylenically-unsaturated carboxylic acid amide; and a said ethylenically-unsaturated optionally-substituted phenyl compound.

Preferably, said first monomer does not include a functional group which is able to hydrogen bond with another functional group of the same type.

Said first monomer is preferably a vinyl monomer.

Said method may involve contacting said first polymeric material with a second monomer. Said second monomer may have any feature of the first monomer described in any statement herein. Preferably, however, the first and second monomers have different functional groups. Preferably, the first monomer is selected so that a functional group that it carries can be reacted with a compound, for example a linker, after said graft polymer has been prepared, so that said compound can be connected to the first polymeric material via the first monomer, whereas under the reaction conditions, the functional group(s) carried by said second monomer do not react so that said compound is not connected to the first polymeric material via the second monomer. Preferably, said second monomer is, therefore, substantially unreactive under conditions wherein said functional group of said first monomer can be reacted. Thus, in the graft polymer, said second monomer may serve to dilute the amount of the first monomer on the surface of the first polymeric material. As a result, the functional groups of the first monomers and, therefore, moieties connected to said functional groups are spaced further apart. Consequently, interference between individual side chains made up of said first monomer (and/or moieties bonded thereto in downstream process steps) may be minimised.

Preferably, said second monomer does not include a substitutable (preferably any) chlorine atom. More preferably, it does not include any halogen atom.

Preferably, said second monomer does not include a carboxylic acid group.

Said second monomer may include a functional group selected from an amide, especially a primary amide, an ether or polyether, or an optionally-substituted aryl, especially a phenyl, group. Said phenyl group may be substituted or unsubstituted. It is preferably unsubstituted.

Said functional group of said second monomer may be linked to the C=C moiety of the monomer directly or by any suitable means. Any type or length of moiety may be provided between said C=C moiety and said functional group. Preferably said functional group is a vinyl group or allyl group. A vinyl group is most preferred.

Preferably, said second monomer is selected from the group consisting of an ethylenically-unsaturated carboxylic acid amide, for example acrylamide; and an ethylenically-unsaturated optionally-substituted (preferably unsubstituted) phenyl compound, for example styrene.

The ratio of said first monomer to said second monomer (if provided) may be in the range 9:1 to 1:9 vol/vol. It is preferably in the range 3:1 to 1:3 vol/vol.

In the method of the seventh aspect, said first polymeric material may be irradiated using any suitable source. Irradiation is suitably carried out in the presence of oxygen, suitably in air. It is believed that irradiation causes free radicals to be created by hydrogen abstraction on the polymer backbone of the first polymeric

material. These radicals combine with oxygen to form peroxide species on the polymeric material which species are stable at ambient temperature (e.g 22°C). Thus, a peroxidized first polymeric material is prepared as a result of said irradiation. Radiation used in said method is suitably ionizing radiation and may comprise gamma radiation, an electron-beam, X-rays, UV radiation, ozonisation or plasma irradiation. The use of gamma radiation is preferred.

The radiation dose may be at least 1 kGy, suitably at least 2 kGy, preferably at least 3 kGy, more preferably at least 4 kGy, especially at least 5 kGy. The dose may be less than 100 kGy, suitably less than 50 kGy, preferably less than 40 kGy, more preferably less than 30 kGy, especially less than 20 kGy. The dose rate may be at least 0.25 kGy/hr, preferably at least 0.5 kGy/hr, more preferably at least 0.75 kGy/hr. The dose rate may be less than 10 kGy/hr, preferably less than 5 kGy/hr, more preferably less than 2.5 kGy/hr, especially less than 2 kGy/hr.

Preferably, in the method, there is an interval after said irradiation and prior to contact with said monomer(s). The irradiated first polymeric material may be stored during the interval, suitably at ambient temperature or below.

Graft polymerisation may be effected by contacting the irradiated first polymeric material with said monomer(s) in a liquid which could be in the form of a solution, partial solution or an emulsion. Said monomer(s) are suitably provided in a solvent which is preferably aqueous and, more preferably, is water. A surface active agent, for example an emulsifying agent may

be included in the solvent, particularly if the monomer(s) are not soluble in water. A homopolymerisation inhibitor, for example ferrous sulphate may be included. The reaction of said monomer(s) and said peroxidized material is preferably carried out in the absence of oxygen and is suitably carried out in an inert, for example a nitrogen, atmosphere.

The concentration of monomer(s) in said liquid may be at least 5 wt%, preferably at least 10 wt%, more preferably at least 15 wt%. The concentration may be less than 50 wt%, preferably less than 40 wt%, especially less than 30 wt%.

In the method, the temperature is preferably raised (preferably to at least 40°C, more preferably to at least 50°C), after said irradiation and when said peroxidized first polymeric material is in the presence of said monomer(s). The temperature is preferably raised to within the range 40 to 60°C, more preferably 40 to 80°C. On raising the temperature, it is believed that the peroxide species decompose, thereby yielding peroxy radicals which can initiate a grafted side chain on reaction with said monomer(s). It will be appreciated that the side chain is covalently bonded to the backbone of the first polymeric material by an -O- bond. This fact can be used to distinguish materials prepared in accordance with the first aspect from materials prepared by a mutual irradiation process since, in the latter, the side chain is bonded to the backbone by a carbon - carbon bond.

Said first polymeric material used in the method may be in any suitable form. For example, it may comprise a powder or pellets (or the like) which may, after

preparation of the graft polymer, be re-shaped, for example by melting, extrusion, blow moulding or other shaping method. Thus, the method of the first aspect may include the additional step of changing the physical form of the graft polymer to make it into a form for use as a solid support. Alternatively, said first polymeric material may be in a form which is usable as a solid support.

Preferably, said first polymeric material is in the form of a fabric which may be woven or non-woven. Said fabric may be as described in any statement herein.

Said fabric is preferably non-woven.

Said graft polymer prepared in the method may have a size in a first dimension of at least 1 cm, preferably at least 2 cm; a size in a second dimension of at least 10 cm, suitably at least 50 cm, preferably at least 100 cm, more preferably at least 200 cm, especially at least 300 cm; and a size in a third dimension of at least 0.1 mm, suitably at least 0.3mm, preferably at least 0.4mm, more preferably at least 0.5mm. The size in the third dimension may be less than 1 cm, suitably less than 0.5 cm, preferably less than 0.2 cm, more preferably less than 0.1 cm, especially less than 0.08 cm.

The degree of grafting may be at least 5%, preferably at least 8%, especially at least 10% by weight. The degree of grafting may be 50% or less, preferably 45% or less, especially 40% or less. The degree of grafting stated is calculated from the weights of the original first polymeric material and the monomer(s) according to the formula

$$\%graft = \frac{wf - wi}{wf} \times 100$$

where wf is the final weight of the graft polymer and wi is the initial weight of the first polymeric material.

The melt flow index (MFI) of the graft polymer may be in the range 0.5 to 15, preferably in the range 0.5 - 5 gram/10 minutes measured according to ASTM D1238.

The method of the seventh aspect may include the step of providing a linker moiety on said graft polymer. The linker moiety is suitably arranged to allow other compounds or moieties to be covalently bonded thereto and/or cleaved therefrom when required. A linker moiety may be synthesized on said graft polymer in a series of steps. Alternatively, said graft polymer may be treated with a linker compound, suitably so that said linker compound becomes covalently bonded to a moiety derived from said one or more monomers or to another moiety linked to a moiety derived from said one or more monomers. Preferably, said linker moiety (however formed) is covalently bonded to a moiety derived from or attached to a said functional group of said monomer(s).

Methods of providing linker moieties are well-known. Examples are described in Tetrahedron Vol.51, No.30, pages 8135 to 8173 (1995) and may include commercially available Wang, Rink and Trityl linkers.

A solid support prepared in a method according to the seventh aspect may be of any known type. For example, WO98/31732 (Irori) describes a range of supports, including wells, trenches, dishes, vessels, beads, pins, crowns and stems. Preferably, however, said support is as

described according to an invention or embodiment described herein.

According to an eighth aspect of the invention, there is provided the use of a graft polymer prepared by irradiating a first polymeric material and subsequently contacting it with one or more monomers, as a solid support for use in synthesis or screening.

According to a ninth aspect of the invention, there is provided a solid support for use in synthesis or screening, the support being prepared or preparable as described according to said seventh aspect.

The method according to said seventh aspect suitably results in the monomer(s) being covalently bonded to the first polymeric material by ether groups. Accordingly, in a tenth aspect, there is provided a solid support for use in synthesis or screening, the support comprising a polymeric backbone comprising a said first polymeric material and pendent side chains derived from one or more said monomers, wherein said side chains are covalently bonded to said first polymeric material by ether linkages.

The presence of said ether linkages can be shown by conventional analytical techniques. Additionally, the support can be treated with neat HI or HBr to cleave moieties derived from said monomer(s) from said first polymeric material.

Said solid support may include a linker moiety as described above covalently linked to said polymeric backbone via pendent side chains which are suitably derived from said monomer(s). Said linker moiety suitably provide binding sites to which other compounds and/or

materials may be covalently bound. For example, said compounds may be starting materials in a sequence of synthetic steps for making chemical compounds.

Advantageously, the solid supports described in any statement herein may be capable of supporting a relatively high loading of material. The loading may be at least 0.01 millimoles/gram, suitably at least 0.1 millimoles/gram, preferably at least 1 millimoles/gram, more preferably at least 2 millimoles/gram, especially at least 3 millimoles/gram. In some cases, 4 millimoles/gram or even 5 millimoles/gram may be supported. It may be possible to support about 10 millimoles/gram in some circumstances. It should be noted that the term "millimole/gram" refers to the amount of material that can be cleaved from the support per gram of the first polymeric material used to make the support. Stated in an alternative manner, the loading may be expressed in micromoles per square centimetre of material (and this is particularly relevant where the support is a laminar material). In this case, the loading may be at least 0.1, suitably at least 1, preferably at least 2, more preferably at least 3, especially at least 4 micromoles per square centimetre. Loadings of up to 10 micromoles per square centimetre have been achieved.

According to an eleventh aspect of the invention, there is provided a method of making a library of compounds, the method starting with an x by y array arrangement of discrete reaction zones, each including an associated identification means for uniquely identifying each zone, wherein adjacent reaction zones in said array arrangement are fixed relative to one another, wherein the sequence of said identification means in said array arrangement is predetermined (hereinafter referred to as

"said predetermined sequence") and wherein the ratio x to y is greater than 10, the method including the steps of:

(a) dividing said array arrangement into a plurality of sub-array arrangements;

(b) subjecting some of said sub-array arrangements to different chemical processes than others;

(c) determining (when required) the identity of each sub-array arrangement by identifying fewer identification means associated with reaction zones in said sub-array arrangement than the total number of identification means associated with reaction zones in said sub-array arrangement;

(d) repeating step (c) (when required) to identify other sub-array arrangements;

(e) optionally dividing respective said sub-array arrangements into a plurality of further sub-array arrangements and repeating steps (b) to (d) on said further sub-array arrangements wherein a reference to "said sub-array arrangement" in steps (b) to (d) is treated as a reference to "said further sub-array arrangement";

wherein the different chemical processes to which each reaction zone is subjected are recorded so that the different chemical processes to which each reaction zone in the library is subjected are known.

The library of compounds may have at least 500, preferably at least 1000, more preferably at least 5000, especially at least 10000 members. However, there is no practical limit within the method or to the number prepared in any one library.

The ratio x to y may be at least 50, suitably at least 100, preferably at least 500, more preferably at least 1000, especially at least 5000.

y is suitably 10 or less, preferably 7 or less, more preferably 5 or less, especially 2 or less. Most preferred is the case wherein y is 1 and, therefore, said array arrangement is a one-dimensional array. x may have any value up to infinity. x is suitably at least 100, preferably at least 1000, more preferably at least 5000, especially at least 10,000.

Said discrete reaction zones may be defined by any suitable means. For example, they could be particulate or may be in the form of a container, such as a microtiter dish or well, or in the form of a continuous surface such as a derivatized glass slide, a silicon chip with a surface adapted for linking of biological particles or molecules, a nitrocellulose sheet, nylon mesh or other such materials, or a hollow or solid surface on which molecules or biological particles are linked, for example MICROTUBE microreactors, sold by Irori and Chiron "pins". Example of suitable means are described in WO98/15825 (Irori).

Preferably, said discrete reaction zones are defined on a laminar material. Said reaction zones may be defined on any material described in any statement herein.

Said identification means may be as described in any statement herein.

The connection of adjacent reaction zones in said array arrangement may be achieved by any suitable means. For example, particulate reaction zones or reaction zones

associated with containers may be strung together. Particles or containers could be manufactured, by extrusion or any other suitably technique, with a connecting web (or the like) between adjacent particles/containers.

Preferably, connection means for connecting adjacent reaction zones is an integral part of (for example unitary with) a means which supports said discrete reaction zones. Said connection means is preferably made substantially of the same material as a part of a means which supports said discrete reaction zones. Where said discrete reaction zones are defined on a laminar material, connection of adjacent reaction zones may be achieved by respective parts of said laminar material extending between adjacent reaction zones.

Recording means is suitably provided for recording said predetermined sequence, preferably electronically. Said recording means preferably comprises a computer.

In step (a), suitably, said array arrangement is divided between a pair of adjacent reaction zones. The division may simply involve cutting the array arrangement between adjacent reaction zones to detach said adjacent reaction zones from one another.

Preferably, on detaching adjacent reaction zones, an indicator means is arranged to distinguish between the ends of the parts thereby formed. Said indicator means is preferably a visual indicator. It may simply comprise an visual identifier, for example a nick (or the like), at or adjacent the end of one of the parts formed. Preferably, said indicator means is arranged to indicate whether an

end is an upstream or downstream (or right or left) end of a sub-array.

Whilst it is possible to determine where to divide the array arrangement (and/or each sub-array arrangement) as described in step (a) and/or (e) at the time the array/sub-array arrangements are to be divided in the course of the preparation of the library of compounds, it is preferred that each division of said array/sub-array arrangement is predetermined as described further below.

Similarly, whilst it is possible to select the chemical processes to which said sub-array arrangements, and/or said further sub-array arrangements, are subjected in steps (b) and/or (e) at the time the sub-array/further sub-array arrangements are to be subjected to said processes and then to record the identity of each sub-array/further sub-array arrangement (or more preferably the identity of each discrete reaction zone in an arrangement) and the reaction to which it (or more preferably each discrete reaction zone) has been subjected, it is preferred that each chemical process to which a sub-array/further sub-array arrangement (or more preferably, each discrete reaction zone) is to be subjected is predetermined as described further below.

Preferably, the position or positions at which said array arrangement is divided in step (a) is/are predetermined. Preferably, a computer is arranged to direct an operator where to divide said array arrangement. Preferably, said array arrangement is divided into the same number of sub-arrays as there are different chemical processes in step (b).

Preferably, in the method, adjacent reaction zones remain fixed relative to (preferably directly to) one another until they are to be subjected to different chemical processes, at which time they are suitably divided as described in step (a). This contrasts with the method described in WO96/16078 (Pfizer) wherein reaction zones which are adjacent in the starting array (e.g. the three dimensional stack of individual sheets) are not all initially fixed to one another.

In step (b), preferably each sub-array arrangement is subjected to a different chemical process compared to each other sub-array arrangement. The different chemical processes suitably comprise reactions with different compounds and/or different reagents.

Preferably, the respective process(es) to which each sub-array arrangement is to be subjected in step (b) is predetermined. Preferably, a computer is arranged to direct an operator as to the process to which each respective sub-array arrangement is to be subjected.

In step (c), the identity of the sub-array arrangements may be determined as described when the identity of a sub-array arrangement is otherwise unknown. For example, if at the start of the method, the array arrangement is divided to define two sub-array arrangements, the identity of each sub-array may be known without the need for the determination in step (c) to be undertaken. However, after subsequent steps, it will be necessary to determine the identity as described in step (c).

In step (c), the identity of less than 50%, suitably less than 25%, preferably less than 10%, more preferably

less than 5% of the total number of reaction zones in said sub-array arrangement is determined, provided that the identity of at least one reaction zone is determined. Suitably, in step (c), the identity of 1 to 10, preferably 1 to 5, more preferably 1 to 2, especially only 1 reaction zone in said sub-array arrangement is determined.

Preferably, in step (c), the identity of each discrete reaction zone in a respective sub-array arrangement is determined by relating the identity of the identification means identified to said predetermined sequence.

Preferably, the method in step (c) comprises:

(i) selecting a reaction zone (hereinafter "said identified reaction zone") to be identified in a selected sub-array arrangement;

(ii) noting the position of said identified reaction zone in said selected sub-array arrangement;

(iii) determining the identity of said identified reaction zone;

(iv) relating the information ascertained in steps (ii) and (iii) to said predetermined sequence thereby to determine the identity of each reaction zone in said sub-array arrangement.

As stated above in said method, the different chemical processes to which each reaction zone is subjected are recorded. Whilst the recording may be done at or about the time each reaction zone is subjected to a particular process (for example just before or just after subjection to a process), preferably, the different chemical processes to which each reaction zone is to be subjected are predetermined and recorded, preferably

before any chemical processes are undertaken, more preferably before the array arrangement is divided in step (a) and/or before any sub-array arrangement is subjected to any chemical process in, for example, step (b).

In one preferred embodiment, a method of making a library of compounds starts with an x by 1 array arrangement (i.e. a one-dimensional array arrangement) of discrete reaction zones, each including an associated identification means for uniquely identifying each zone and adjacent reaction zones of the arrangement being fixed to one another with the sequence of the identification means in said array arrangement being predetermined and preferably stored electronically, for example in a computer, wherein each process to which each respective reaction zone is to be subjected is predetermined and preferably recorded electronically, for example in said computer, the method including the steps of:

(A-1) dividing said array arrangement in a predetermined manner so as to provide a plurality of predetermined sub-array arrangements;

(B-1) subjecting said sub-array arrangements to predetermined, preferably chemical, processes;

(C-1) selecting a sub-array arrangement and determining its identify by identifying only one reaction zone of the sub-array arrangement (preferably a reaction zone at one end of the sub-array arrangement) in order to enable the determination of the next procedure (for example a further division as described in (B-1)) to which said selected sub-array arrangement is to be subjected.

Preferably, said computer outputs information to an operator to direct the next procedure to which the selected array is to be subjected in step (C-1).

Step (C-1) may be undertaken prior to step (B-1) in order to ensure that the sub-array arrangements are subjected to the appropriate predetermined chemical processes. Step (C-1) may be repeated for each sub-array arrangement subjected to chemical processes in step (B-1). Step (C-1) may be repeated after the next procedure described in step (C-1) has been undertaken.

Sub-array arrangements may be pooled for washing purposes (or other procedures common to a plurality of sub-array arrangements). Advantageously, the sub-array arrangements may be selected and identified as described in step (C-1) after such common procedures.

In a less preferred embodiment, a method of making a library of compounds starts with an x by 1 array arrangement of discrete reaction zones, each including an associated identification means for uniquely identifying each zone and adjacent reaction zones of the arrangement being fixed to one another with the sequence of the identification means in said array arrangement being predetermined and preferably stored electronically, for example in a computer, the method including the steps of:

(A-2) dividing said array arrangement into a plurality of sub-array arrangements;

(B-2) subjecting said sub-array arrangements to processes which are preferably chemical processes;

(C-2) selecting a sub-array arrangement (either before or after step (B-2)) and determining its identity by identifying only one reaction zone of the sub-array arrangement (preferably a reaction zone at one end of the sub-array arrangement)and using the information available

(e.g. the sequence of the identification means, the position of the reaction zone identified and/or the number of reaction zones in said sub-array arrangement) to identify each reaction zone in said sub-array.

(D-2) recording each process to which each reaction zone is subjected, suitably just prior to or just after a reaction zone has been subjected to a process.

After all of the relevant process steps have been undertaken in the method according to the eleventh aspect, a library of compounds bound to respective discrete reaction zones may be provided. The compounds may then be cleaved from the discrete reaction zones. It will be appreciated that, at the end of the method, the processes to which each reaction zone has been subjected will be known and, therefore, the identity of each compound cleaved from each reaction zone can be determined.

According to a twelfth aspect of the invention, there is provided a library of compounds made using a method according to the eleventh aspect.

The method described in the eleventh aspect which is used to identify each reaction zone in a sub-array arrangement is believed to be novel and, accordingly, in a thirteenth aspect, the invention provides a method of determining the identity of each reaction zone in a sub-array arrangement comprising a known number of reaction zones wherein said sub-array arrangement has been detached from a parent array arrangement wherein the identity and position of each reaction zone in the parent array arrangement has been predetermined, the method comprising:

(a) selecting a reaction zone (hereinafter "said identified reaction zone") to be identified in said sub-array arrangement;

(b) noting the position of said identified reaction zone in said sub-array arrangement;

(c) determining the identity of said identified reaction zone;

(d) relating the information ascertained in steps (b) and (c) to the predetermined identity and position of each reaction zone in the parent array arrangement, thereby to determine the identity of each reaction zone in said sub-array arrangement.

The invention extends to a method of making a library of chemical compounds which allow synthesis on a much larger scale compared to techniques used hitherto, material quantities in the 1 to 5 mg range being easily handled. The invention provides a method of making a laminar material suitable for combinatorial library generation, the material having a high loading capacity and being easily handled. The invention may use a laminar material of micro-filamentous construction leading to novel and hitherto unrecognised advantages. For example, due to the enormously increased surface area of micro-filamentous laminar material, the resultant available chemical functionality per unit area is much increased. This makes the preparation of multi-milligram quantities possible on a small area of laminar material, for example 50 mg of a set of combinatorial products may each be prepared on approximately 2 cm^2 of the materials. In the method, a sample of polyethylene, polypropylene or other polyolefins of appropriate type in bulk powder form is irradiated by a ^{60}Co source and subsequently separately functionalised by polymer co-grafting with an appropriate monomer. Available chemistry functionality on the bulk

powder polymer co-grafted polyolefin is then accessed by methods well described in chemical literature. The functionalised bulk-powder polymer co-grafted polyolefin may be melted, extruded, blow moulded, shaped, formed in any physical form necessary. These may take the form of small porous containers, tape, strip or streamer, laminar sheet and "pins and crowns", and microfilamentous sheet.

Any feature of any aspect of any invention or embodiment described herein may be combined with any feature of any other aspect of any other invention or embodiment described herein.

Specific embodiments of the invention will now be described, by way of example, with reference to the accompanying diagrammatic drawings, in which:

Figure 1 is a side view of a fragment of a string of pouches;

Figure 2 is a cross-section along line II-II of Figure 1;

Figure 3 (a) to (e) show stages in the manufacture of a string of pouches each of which includes an encapsulated Rf tag;

Figure 4 (a) to (d) are respective cross-sections along lines A-A, B-B, C-C and D-D of figure 3;

Figure 5 shows cut ends of a string of pouches; and

Figure 6 shows the sequence of steps for using a string of pouches for making a library of compounds.

Example 1

Samples (3 cm by 10 cm) of polypropylene non-woven fabric (sold under the Trade Mark LUTRASIL by Freudenberg Spinnvliesstoffe KG; having a density of 100 g/m^2; and a thickness of 550 to 650 μm) were irradiated in air in a Cobalt 60 gamma radiation source to total doses of 2.5 kGy to 10 kGy and at a dose rate of 1 kGy/hr. Following irradiation, accurately weighed samples were placed in glass vessels together with 100ml of an aqueous solution comprising methacrylic acid (MAA) and dimethylacrylamide (DMAM) at ratios varying from 10/0 to 1/9 %vol/vol and ferrous sulphate as a homopolymerisation inhibitor. The mixtures were deoxygenated by bubbling with oxygen free nitrogen and the glass vessels were placed in a thermostatted water bath under nitrogen for 3 hours at 70°C. The grafted fabrics were filtered from the grafting solution, washed thoroughly with warm deionised water and dried to a constant weight. The degree of grafting was calculated as follows:

$$\%\text{Graft} = \frac{wf - wi}{wi} \times 100$$

where wi is the initial weight of the preirradiated sample; and
wf is the resultant weight of the grafted sample.

Table 1 below gives the percentage graft weights obtained for the different irradiation doses and at varying monomer ratios.

Table 1

Run No	TOTAL DOSE				MAA/DMAM
	2.5 kGy % graft weight	5.0 kGy % graft weight	7.5 kGy % graft weight	10 kGy % graft weight	% vol/vol
1	22.5	22.24	42.66	57.32	10/10
2	16.19	24.95	35.34	45.86	9/1
3	12.41	16.81	22.9	29.86	8/2
4	8.35	12.18	16.09	20.19	7/3
5	8.23	9.92	13.48	16.59	6/4
6	5.0	5.86	8.37	8.63	5/5
7	2.42	3.36	4.97	5.27	4/6
8	1.63	2.27	3.09	3.35	3/7
9	0.85	1.33	1.73	2.38	2/8
10	0	0.32	0.35	0.61	1/9

Example 2

Polypropylene fabric as described in Example 1 was preirradiated by gamma irradiation as described in Example 1 to a total dose of 25 kGy at a dose rate of 1kGy/hr, then grafted with a % vol/vol styrene/4-chloromethylstyrene aqueous emulsion containing 0.1% of an emulsifying agent (dodecyl-benzene sulphonic acid sodium salt (ex BDH)) at varying ratios of 8:2, 7:3, 6:4, 5:5 %vol/vol of styrene:chloromethylstyrene by reaction for 5 hours at 80°C. The grafted fabric samples were filtered from the grafting solution, washed thoroughly with warm deoxidised water, followed by soxhlet extraction in acetone. The samples were dried to a constant weight and the respective graft weights were 10.2%, 8.8%, 8.3% and 9.4%.

Example 3

A polypropylene non-woven fabric as described in Example 1, peroxidised under the same conditions as above, was grafted in a 10 %vol/vol aqueous solution containing methyl methacrylate/dimethyl acrylamide at a ratio of 6:4 %vol/vol, using Triton X-114 (an octyl-phenoxy polyethoxyethanol (ex BDH)) as an emulsifying agent and at a temperature of 80°C for 5 hours. The grafted fabric, after washing with warm deionised water and extraction with acetone, gave a degree of grafting of 30.4%.

Example 4

Polypropylene powder, peroxidised under the same conditions as above, was grafted in an 10 %vol/vol aqueous solution containing acrylic acid/dimethyl acrylamide at a ratio of 6:4 %vol/vol and 5.56g/l of ferrous sulphate as

a homopolymerisation inhibitor at 80°C for 5 hours. The grafted polypropylene powder was filtered from the grafting solution, washed thoroughly with warm deionised water until neutrality and dried to a constant weight. The degree of grafting was found to be 38.33%.

Example 5

Polypropylene pellets Novolen 2800J (exBASF) were moulded by compression moulding into a plaque of 1500 micron thickness, cut into small dumbells of 33mm x 3mm and peroxidised in a gamma source for a total dose of 25 kGy at a dose rate of 1 kGy/hr. The peroxidised polymer was grafted in a 10 %vol/vol aqueous solution of acrylic acid/dimethyl acrylamide at a ratio of 6:4 %vol/vol, using ferrous sulphate as a homopolymerisation inhibitor for 5 hours at 80°C. The resulting grafted polymer was washed thoroughly and dried to constant weight. The degree of grafting was found to be 29.57%.

Example 6 - Preparation of long length of grafted material

The procedures of Examples 1 to 3 may be used, generally, to provided long lengths of grafted material. In this regard a strip (which could have a length of the order of 6 metres long and a width up to 30 cm) is wound up into a roll and irradiated to peroxidize it. The peroxidized material is stable for up to about 3 months at ambient temperature (about 22°C). The roll of material can be unrolled and contacted with a non-woven interlayer material and re-rolled. It may then be immersed in the monomer(s) solution and the reaction undertaken as in Example 1. The provision of the interlayer aids contact

of the monomer(s) solution with the peroxidized polypropylene and penetration of it thereinto.

Examples 7 to 19 - Reactions undertaken on grafted materials.

The following reactions were undertaken to show that materials prepared as described herein can be used as solid supports. The following abbreviations are used hereafter:

Boc - tert-butyloxycarbonyl
DIC- Di-isopropylcarbodiimide
HOBt - N-Hydroxybenztriazole
TFA - trifluoroacetic acid
DCM - dichloromethane
Fmoc - 9-fluorenylmethoxycarbonyl
DMF - N,N'-dimethylformamide

Example 7 - Derivatisation of acrylic acid grafted material

An acrylic acid grafted material (2 meters, 0.75 Mrad, 6:4 methacrylic acid: dimethylacrylamide grafting) was reacted with Boc-NH-$(CH_2)_2$-NH_2/DIC-HOBt(10 equiv.) in dichloromethane for 48 hours. After the general wash cycle described in Example 19 below, the Boc group was removed with 50% TFA in DCM. The amino compound was then reacted with the freshly prepared anhydride of the diacid 3,6,9-trioxaundecanedioic acid (20 equiv) in DCM for 48 hours. The resulting carboxy derivative was then coupled to Boc-NH-$(CH_2)_2NH_2$/DIC-HOBt (10 equiv) in DCM for 48 hours. The Boc group was then removed as above and a quantitative ninhydrin test gave a substitution of 2.35 μmol/cm^2.

200 cm^2 of the material (2.35 $\mu mol/cm^2$) were reacted with Fmoc-Gly/DIC-HOBt for 1 hour in DMF. The resin was then capped with Ac_2O/pyridine in DCM for 2 hours. A quantitative Fmoc test gave a substitution of 1.42 $\mu mol/cm^2$. The derivatised material was treated with 20% piperidine in DMF for 20 minutes. The free amino derivative was then treated with a solution of p-[(R,S)-α-[1-(9H-Fluoren-9-yl)-methoxyformamido]-2,4-dimethoxybenzyl]-phenoxyacetic acid (Fmoc-rink linker, 1.5 eq), DIC (1.5 eq), HOBt (1.5 eq) in DCM and the resin shaken overnight. The remaining free amino sites were capped with excess acetic anhydride/pyridine in DCM.

Example 8 - Preparation of the tripeptide Fmoc-Ala-Phe-Gly-NH_2

90 cm^2 of the Fmoc-Rink linker-material prepared in Example 7 was treated with 20% piperidine in DMF for 20 minutes. The resulting amino compound was treated with Fmoc-Phe-Gly-OH (4 eq), HOBt (4 eq) and DIC (4 eq) in DCM for 24 hours. The Fmoc group was then removed and the same procedure was used to couple Fmoc-Ala to obtain Fmoc-Ala-Phe-Gly-Rink linker-material. The tripeptide was then cleaved from the resin by shaking with 95% TFA, 5% H_2O for one hour. The crude material was first purified on silica and then on semi-prep HPLC to provide 1.7 mg pure tripeptide (38% yield). The tripeptide was confirmed by NMR data, ES MS (MH) 415. It co-eluted with an authentic sample which was prepared on ordinary polystyrene beads.

Example 9 - Oxidation Experiment

50 cm^2 of Fmoc-Rink linker-material (0.316$\mu mol/cm^2$) prepared as described in Example 7 was treated with 20% piperidine in DMF for 20 minutes. Fmoc-Phenylalanine

(5eq), HOBt (5eq), DIC (5eq) were added and the coupling reaction run for 6 hours in DCM. 25 cm^2 of the material was treated with 20% piperidine in DMF for 20 minutes to remove the Fmoc group and the same coupling procedure as above was then used to couple 4-hydroxymethyl benzoic acid. 4 cm^2 of the 25 cm^2 piece of material was treated with 95% TFA to obtain the starting material. The rest of the resin was suspended in dry DMSO (10 ml) and to this was added pyridine sulphurtrioxide (10 eq), triethylamine (10 eq) and the reaction was shaken for 18 hours. Cleavage with 95% TFA and HPLC analysis revealed complete conversion to the aldehyde product (confirmed by ES MS, MH 297 and co-elution with an authentic sample). (51% pure, impurity is HOBt).

Example 10 - Reduction Experiment

25 cm^2 of Fmoc-Phe-Rink-linker-material as prepared in Example 9 was treated with 20% piperidine in DMF for 20 minutes to remove the Fmoc group. The resulting amino product was then coupled to 4-formylbenzoic acid (5eq), DIC (5eq), HOBt (5eq) in DCM for 2 hours. 4 cm^2 was cleaved with 95% TFA to provide the starting standard. The rest of the resin was suspended in MeOH (10ml) and treated with sodium cyanoborohydride (10 eq), (a trace of bromocresol green was added to monitor the pH which was maintained by periodic addition of 10% HCl in ethanol (one or two drops at a time)). After sixteen hours, the resin was washed as described in Example 19 and cleavage with 95% TFA revealed complete conversion to the alcohol product as shown by HPLC analysis. ES MS (MH 299) and co-elution with an authentic sample confirmed the alcohol. (39% pure, impurity HOBt).

Example 11 - Suzuki Experiment

30 cm^2 of Fmoc-Rink-linker-material (0.316 μmol/cm^2), prepared as described above, was treated with 20% piperidine in DMF for 20 minutes. The resulting amino compound was then coupled to Fmoc-glycine (5 eq), DIC (5 eq), HOBt (5 eq), in DCM for 3 hours. A ninhydrin test was negative. The Fmoc group was then removed as described above and the resulting amino product was coupled to 4-iodobenzoic acid (5 eq), HOBt (5 eq), and DIC (5 eq) in DCM. The reaction was shaken for 16 hours. 4 cm^2 was treated with 95% TFA to provide the starting standard. The remaining resin was swollen in DMF (20 ml) and then phenylboronic acid (1.5 eq), $Pd[P(Ph)_3)]_4$ (0.1 eq) and K_2CO_3 (2 eq) were added. The reaction was heated at 60°C for 6 hours. The reaction medium became black, but the resin washed well using the procedure described in Example 19. It was then cleaved with 95% TFA for 1 hour and the crude material analysed by HPLC. (35% conversion, ES MS 255, longer reaction time improved conversion).

Example 12 - Derivatisation of styrene /chloromethylstyrene grafted material

The styrene/chloromethylstyrene (5:5, 9.4% graft weight) material (30 cm^2) prepared as described in Example 2 was suspended in DMF (50 ml). Potassium phthalimide (10 eq) was added and the reaction stirred gently at 120°C for 24 hours. The material was washed with hot DMF (5x), DMF:H_2O (1:1,5x), Dioxan:H_2O (1:1, 5x), Dioxan (5x), DCM (5x), and ethyl ether (5x).

The material was then suspended in ethanol (50 ml), hydrazine hydrate (5 ml) was added and the reaction refluxed for 4 hours. It was washed as described in

Example 19 to yield the amino derivative which gave a substitution of 1.9 μmol/cm^2. This material was used to prepare the tripeptide of Example 8 by the same procedure (95% pure, in quantitative yield).

Example 13 - Derivatisation of styrene/chloromethylstyrene grafted material

Styrene/chloromethylstyrene (5:5, approx 20% graft weight) material (100cm^2) was derivatised to the aminomethyl derivative. It gave a substitution of 1.35 μmol/cm^2.

Example 14 - Preparation of Fmoc-Phe-Rink linker-material

90 cm^2 of the aminomethyl material of Example 13 was then reacted with Fmoc-Rink-linker (1.5 eq), DIC (1.5 eq), HOBt (1.5 eq) in DCM for 16 hours. A ninhydrin test was negative. An Fmoc test gave a substitution of 1.25 μmol/cm^2. The Fmoc group was removed with 20% pipridine in DMF and the resulting amino product coupled to Fmoc-Phenylalanine (5 eq), DIC (5 eq), HOBt (5 eq) for 4 hours. A ninhydrin test was negative.

Example 15 - Reduction Experiment

25 cm^2 of Fmoc-Phe-Rink linker-material as prepared in Example 14 was treated with 20% piperidine in DMF for 20 minutes to remove the Fmoc group. The resulting amino product was coupled to 4-formylbenzoic acid (5 eq), DIC (5 eq), HOBt (5 eq) in DCM for 2 hours. After a wash cycle as described in Example 19, the material was suspended in MeOH (10 ml) and treated with sodium cyanoborohydride (10 eq), (a trace of bromocresol green was added to monitor

the pH which was maintained acidic by periodic addition of 10% HCl in ethanol (one or two drops at a time)). After 16 hours, the resin was washed and cleavage with 95% TFA revealed complete conversion to the alcohol product (ES MS, MH 299).

Example 16 - Suzuki Experiment

25 cm^2 of Fmoc-Rink linker-material was treated with 20% piperidine in DMF for 20 minutes to remove the Fmoc group. The resulting amino compound was then coupled to Fmoc-glycine (5 eq), DIC (5 eq), HOBt (5 eq) in DCM for 3 hours. A ninhydrin test was negative. After removal of the Fmoc group as above, the amino product was coupled to 4-iodobenzoic acid (5 eq), DIC (5 eq), HOBt (5 eq) in DCM. The reaction was complete after 4 hours. The material, suspended in DMF (25 ml), was treated with phenylboronic acid (1.5 eq), $Pd[P(Ph)_3]_4$ (0.1 eq) and K_2CO_3 (2 eq) were added. The reaction was heated at 100°C for 16 hours. After the wash cycle of Example 19 and cleavage with 95% TFA, HPLC revealed complete conversion of starting material to product (ES MS, MH 255).

Example 17 - Derivatisation of styrene/chloromethylstyrene grafted material with a Wang linker

25 cm^2 of the styrene/chloromethylstyrene (5:5, about 20% graft weight) material was suspended in acetonitrile (30 ml). 4-Hydroxybenzaldehyde (0.5g, 4 mmol), K_2CO_3 (1.1g, 8mmol)) were added followed by sodium iodide (0.6g, 4mmol)). The mixture was refluxed for 16 hours. The material was washed as described in Example 19 and then reduced with sodium cyanoborohydride in methanol as was

described earlier to produce the material derivatised with Wang linker.

Example 18 - Preparation of Fmoc-Phe-Gly-OH

The Wang material prepared above was reacted with Fmoc-Glycine (0.3g, 1mmol), DIC (1mmol), DMAP (0.1mmol) in DCM for 24 hours. A quantitative Fmoc test gave a substitution of 2.34 μmol/cm^2. The Fmoc group was removed with 20% piperidine in DMF and the resulting amino compound coupled to Fmoc-Phenylalanine (0.39g, 1 mmol), DIC (1 mmol), HOBt (1 mmol) in DCM for 4 hours. The material was then treated with 95% TFA and the crude analysed on HPLC to reveal the desired dipeptide (ES MS, MH445) as the only major compound.

Example 19 - General Wash Cycle

This cycle was used after every chemical operation done on a material: DMF (5x), DCM (5x), MeOH (5x) and DCM (5x).

Example 20 - Manufacture of a string of pouches

A string 2 of pouches 4 is shown in figures 1 and 2. The pouches 4 are rectangular and have a dimension "x" of about 30 mm and a dimension "y" of about 15 mm and comprise two layers of material (each layer having a thickness of 550 to 650 μm) arranged to define an internal region 6 which is bounded by fold line 8, top weld 10 and respective transverse welds 12. A respective generally cylindrical Rf tag 14 is retained in each of the internal regions 6.

The Rf tags are 12 mm RfID tags ("Avid tags") obtained from Selecta Tag of Kent, England. Each tag possesses a unique encoded number which cannot be altered. The tags are arranged to be read by use of a reading device which emits a radio frequency which activates a respective tag to cause it to transmit its encoded number to a detector. During the manufacturing process or thereafter, each tag is read and its number recorded in a computer so that the order of the tags along the entire string is known.

The string of pouches may be manufactured using a machine (not shown) which carries out the steps described below with reference to Figures 3 and 4.

A long strip 20 of grafted polymer prepared as described in Example 6 is fed into a machine (not shown) (see figures 3(a) and 4(a)). A region of the strip extending from its leading end 22 is then folded in half (see figures 3(b) and 4(b)) and is then ultrasonically welded transversely at (or close to) the leading end to define one transverse weld 12 (see figures 3(c) and 4(c). A tag 14 is then dropped into the half-formed pouch (see figure 3(d)) and, thereafter, pouch 8 is completed by ultrasonic welding to define top weld 10 and the other transverse weld 12 (see figures 3(e) and 4(d)). The process is then continued from the step shown in figure 3 (d) to manufacture a long string comprising any desired number of individual pouches, each containing a tag 14.

It should be noted that the transverse welds 12 are of sufficient thickness so that the string may be dissected by cutting centrally along the welds, without affecting the integrity of the welds and/or the ability of the pouches disposed adjacent to the cut ends to retain

tags within their internal regions. When the string is dissected, the cut ends may be distinguished from each other, for example by being marked by suitable means - one may include a nick 13 as shown in figure 5.

Thus, it should be appreciated that the method described above provides a simple means of providing an infinitely long continuous strip of individual and uniquely identifiable support sites for solid-phase synthesis, with the position of each support site within the strip being predetermined.

Example 21 - Method of making a library of compounds

The following steps may be involved in making a library of compounds:

(a) The size of the library to be made is predetermined and this predetermines the number of pouches to be included in the string of pouches used in the method. A string of pouches of the required length is selected and the right hand end tag of the string is read to determine the number encoded by its Rf tag. (The right hand end tag may be identified simply be being the tag which does not have a nick as shown in figure 5). Since as described in Example 7 the order of the tags along the whole string manufactured is known, by knowing the identity of the right hand end tag, the identity of each tag and its exact position in the selected string of pouches will be known. Additionally, the identity of each compound and the particular pouch on which each compound is to be made are predetermined. The methodology for preparing the compounds on the appropriate pouches is also predetermined.

Information on the aforementioned is stored in a computer which is programmed to provide an output to an operator to direct the steps for making the library.

(b) The computer then directs the steps to be undertaken. For example, referring to figure 6, at stage (i), the string 2 may be reacted with compound A# so that a group A is attached to each pouch in the string, as represented at stage (ii).

(c) The computer then directs where the string 2 is to be cut. It may be cut in half, into thirds, or in any predetermined manner required. Determining the correct position for the division may be achieved by an operator counting the number of pouches to the position of division or by measuring the length of the string to the position. The string is cut along the appropriate transverse weld 12 and an identifier is used (for example a nick as shown in figure 5) to enable an operator to distinguish between the right hand and left hand ends of the resulting strings which are represented at stage (iii).

(d) One string at stage (iii) may be reacted with a compound B# and the other with a compound C# so that groups AB and AC are attached to respective strings as shown at stage (iv).

(e) The strings at stage (iv) may be pooled and subjected to a wash cycle.

(f) After the wash cycle, each string may be individually selected by an operator and the respective right hand end tags read to determine the identity of the respective strings. The computer then directs the next

procedure to which the respective strings are to be subjected.

(g) At stage (v), the respective strings may be reacted with compounds D#, E#, F# and G# so that groups ABD, ABE, ACF and ACG are attached to respective strings as shown at stage (vi).

(h) The strings at stage (vi) may be pooled and subjected to a wash cycle. Thereafter, all the strings may be reacted with a compound H# and subjected to a wash cycle so that groups ABDH, ABEH, ACFH and ACGH are attached to respective strings as shown at stage (vii).

(i) The procedure described in (f) above may then be undertaken and other compounds may be reacted as directed by the computer according to the predetermined methodology.

(j) At the end of the procedure each compound may be cleaved from the pouches and directed to a respective container which includes a marker which is associated with the Rf tag contained within the pouch from which the respective compound was cleaved. Thus, the operator can identify a marker and, from this, use the computer to determine the identity of the compound and/or the process steps used in its preparation.

Each compound prepared may subsequently be tested and/or analysed and further details relating thereto entered into the computer.

The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and

which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

CLAIMS

1. A method of supporting a compound or other moiety, the method using a fabric which comprises a plastics material.

2. A method according to claim 1, wherein said fabric comprises filaments having a diameter of at least 5 μm.

3. A method according to claim 1 or claim 2, wherein said filaments have a diameter of 500 μm or less.

4. A method according to any preceding claim, wherein said fabric has a density of at least 20 g/m^2.

5. A method according to any preceding claim, wherein said density is less than 250 g/m^2.

6. A method according to any preceding claim, wherein said fabric is laminar.

7. A method according to any preceding claim, wherein said fabric is a graft polymer.

8. A method according to claim 7, wherein said graft polymer is prepared by irradiating a first polymeric material and subsequently contacting it with one or more monomers.

9. A method according to claim 7 or claim 8, wherein said graft polymer includes a functional group capable of undergoing a reaction with an electrophilic or nucleophilic moiety.

10. A method according to claim 9, wherein said functional group is selected from optionally-substituted aryl and heteroaryl groups, carboxylic acid, carboxylic acid derivatives, amines, amine derivatives, inorganic acid, sulphate, hydroxy and substituted alkyl, cycloalkyl and cycloheteroalkyl groups and protected versions of any of the aforesaid.

11. A method according to any preceding claim, wherein said fabric includes a linker moiety which is arranged to allow other compounds or moieties to be covalently bonded thereto and/or cleaved therefrom when required.

12. The use of a fabric as a solid support for supporting a compound or other moiety.

13. A solid support for supporting a compound or other moiety, said solid support comprising a fabric.

14. A solid support according to claim 13, including a linker moiety which is arranged to allow said compound or other moiety to be covalently bonded to the support and/or cleaved therefrom when required.

15. A solid support according to claim 13 or claim 14, wherein said support defines a plurality of distinct regions for supporting different compounds or moieties.

16. An invention according to any of claims 1 to 15, wherein an identification means is associated with said fabric.

17. A solid support for supporting a compound or other moiety, the support being flexible and including means

(hereinafter "enclosure means") defining an enclosed region.

18. A solid support according to claim 17, wherein said support is as described in any of claims 13 to 16.

19. A solid support according to claim 17 or claim 18, wherein an identification means or a resin is arranged within said enclosed region.

20. A solid support according to any of claims 17 to 19, made of a laminar material having a thickness of at least 100 μm and less than 5000 μm.

21. A solid support according to any of claims 17 to 20, wherein said enclosed region has a variable volume and/or a variable three-dimensional shape.

22. A solid support according to any of claims 13 to 21, said support comprising an elongate string of enclosed regions.

23. A method of manufacturing a solid support according to any of claims 17 to 22, the method comprising causing a flexible material to define said enclosed region.

24. Apparatus for use in a method according to claim 23, the apparatus comprising:

feeding means for feeding an elongate strip of material;

folding means for folding the elongate strip; and

securing means for securing parts of the strip together to define an enclosed region.

25. A method of making a solid support for use in synthesis or screening, the method comprising irradiating a first polymeric material and subsequently contacting it with one or more monomers in order to prepare a graft polymer.

26. A method according to claim 25, wherein said first polymeric material is selected from an optionally-substituted polyolefin, polyamide, polyurethane, polyester or a copolymer of ethylenically-unsaturated comonomers.

27. A method according to claim 25 or claim 26, wherein said first polymer is ethylenically-unsaturated and includes a functional group capable of undergoing an electrophilic or nucleophilic reaction.

28. A method according to any of claims 25 to 27, wherein said method involved contacting said polymeric material with both a first monomer and a second monomer, wherein said first monomer is selected so that a functional group that it carries can be reacted with a compound after said graft polymer has been prepared so that said compound can be connected to said first polymeric material via the first monomer, whereas under the reaction conditions, the functional groups carried by said second monomer do not react so that said compound is not connected to the first polymeric moiety via the second monomer.

29. The use of a graft polymer prepared by irradiating a first polymeric material and subsequently contacting it with one or more monomers, as a solid support for use in synthesis or screening.

30. A solid support for use in synthesis or screening, the support being prepared or preparable as described in claim 28.

31. A method of making a library of compounds, the method starting with an x by y array arrangement of discrete reaction zones, each including an associated identification means for uniquely identifying each zone, wherein adjacent reaction zones in said array arrangement are fixed relative to one another, wherein the sequence of said identification means in said array arrangement is predetermined (hereinafter referred to as "said predetermined sequence") and wherein the ratio x to y is greater than 10, the method including the steps of:

(a) dividing said array arrangement into a plurality of sub-array arrangements;

(b) subjecting some of said sub-array arrangements to different chemical processes than others;

(c) determining (when required) the identity of each sub-array arrangement by identifying fewer identification means associated with reaction zones in said sub-array arrangement than the total number of identification means associated with reaction zones in said sub-array arrangement;

(d) repeating step (c) (when required) to identify other sub-array arrangements;

(e) optionally dividing respective said sub-array arrangements into a plurality of further sub-array arrangements and repeating steps (b) to (d) on said further sub-array arrangements wherein a reference to "said sub-array arrangement" in steps (b) to (d) is treated as a reference to "said further sub-array arrangement";

wherein the different chemical processes to which each reaction zone is subjected are recorded so that the different chemical processes to which each reaction zone in the library is subjected are known.

32. A method according to claim 31, wherein said array arrangement is an x by 1 array arrangement (i.e. a one-dimensional array arrangement) of discrete reaction zones, each including an associated identification means for uniquely identifying each zone and adjacent reaction zones of the arrangement being fixed to one another with the sequence of the identification means in said array arrangement being predetermined, wherein each process to which each respective reaction zone is to be subjected is predetermined, the method including the steps of:

(A-1) dividing said array arrangement in a predetermined manner so as to provide a plurality of predetermined sub-array arrangements;

(B-1) subjecting said sub-array arrangements to predetermined processes;

(C-1) selecting a sub-array arrangement and determining its identify by identifying only one reaction zone of the sub-array arrangement in order to enable the determination of the next procedure to which said selected sub-array arrangement is to be subjected.

33. A method of determining the identity of each reaction zone in a sub-array arrangement comprising a known number of reaction zones wherein said sub-array arrangement has been detached from a parent array arrangement wherein the identity and position of each reaction zone in the parent array arrangement has been predetermined, the method comprising:

(a) selecting a reaction zone (hereinafter "said identified reaction zone") to be identified in said sub-array arrangement;

(b) noting the position of said identified reaction zone in said sub-array arrangement;

(c) determining the identity of said identified reaction zone;

(d) relating the information ascertained in steps (b) and (c) to the predetermined identity and position of each reaction zone in the parent array arrangement, thereby to determine the identity of each reaction zone in said sub-array arrangement.

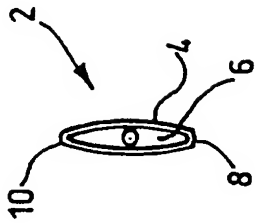


Fig.2.

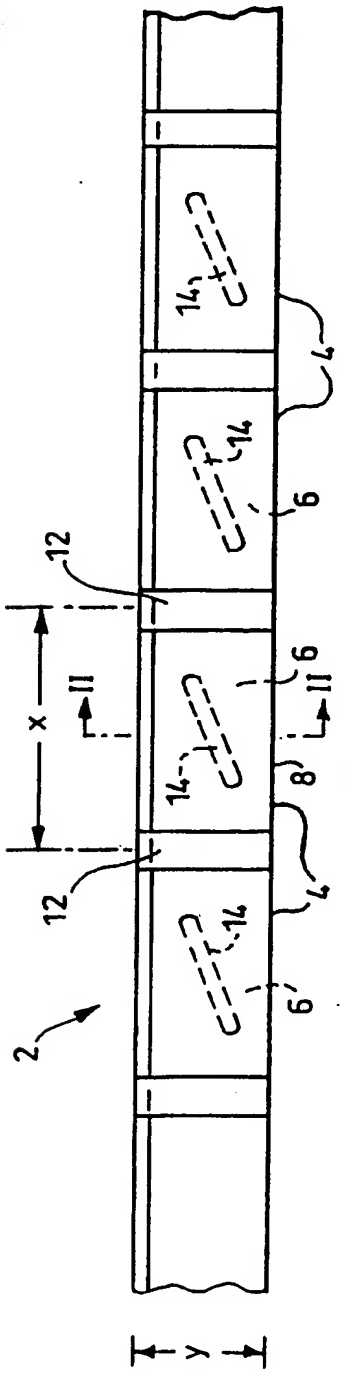


Fig.1.

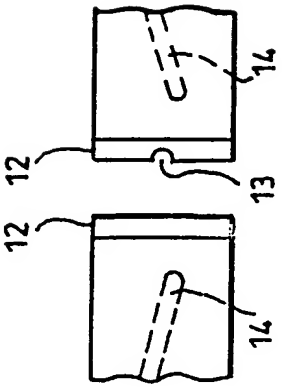


Fig.5.

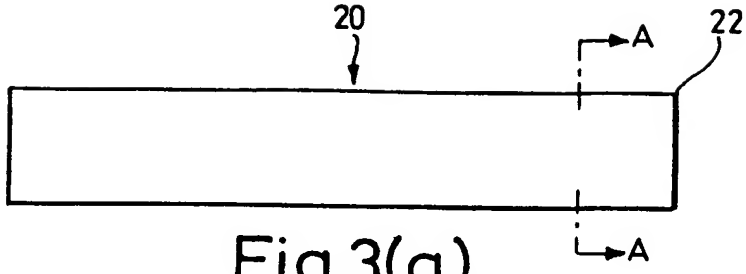


Fig.3(a)

Fig.4(a)

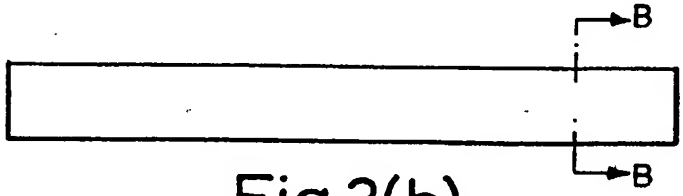


Fig.3(b)

Fig.4(b)

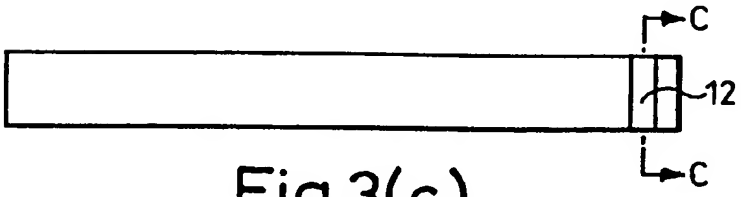


Fig.3(c)

Fig.4(c)

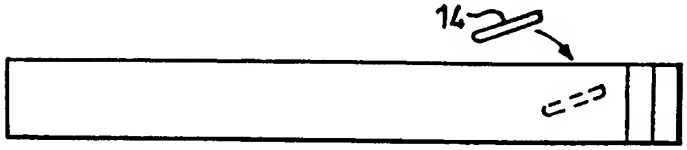


Fig.3(d)

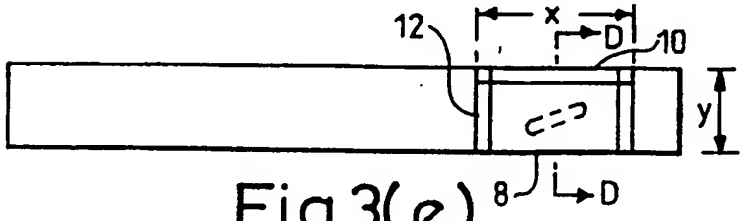


Fig.3(e)

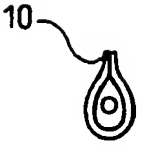
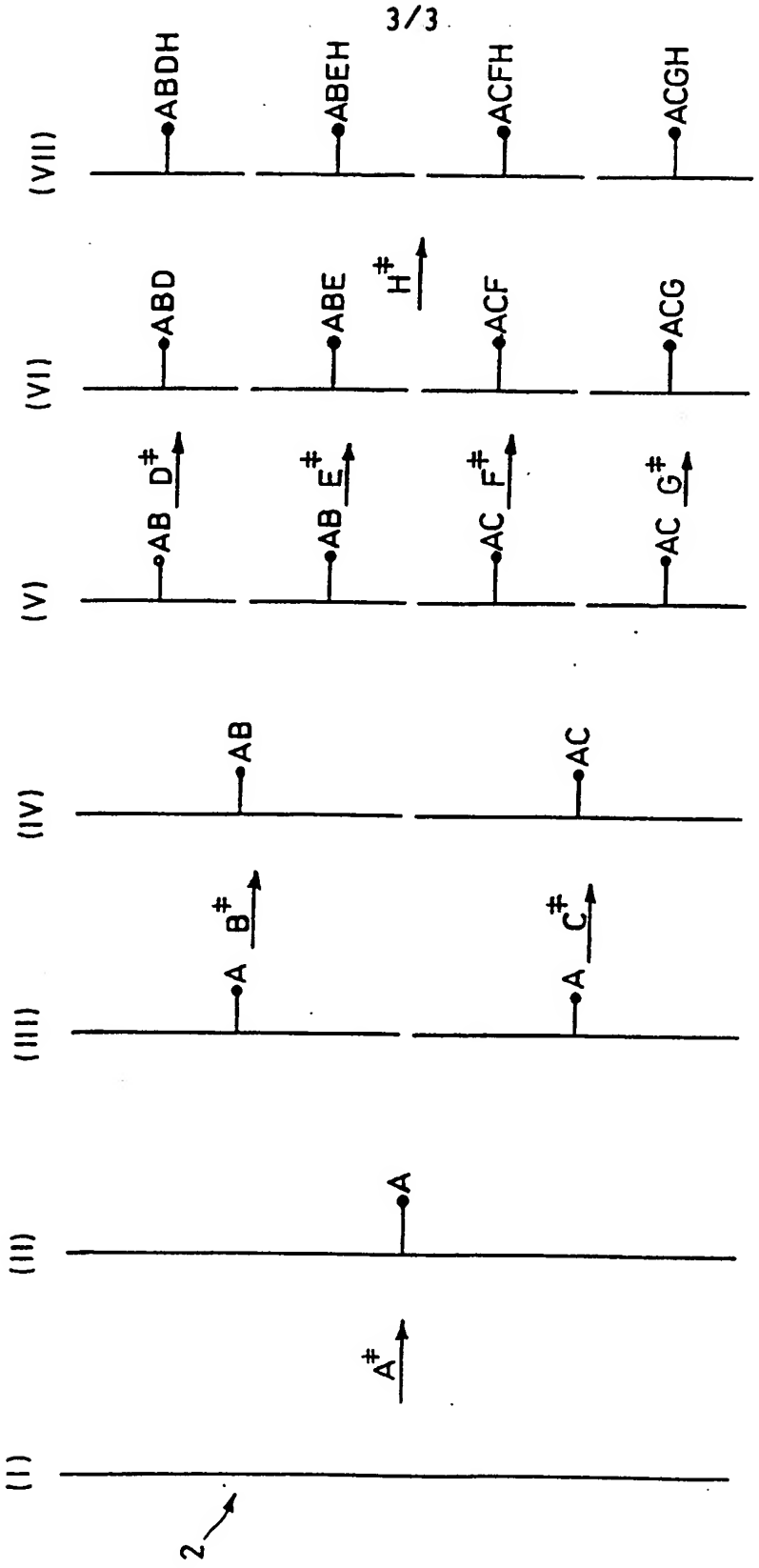


Fig.4(d)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AC G#
(V)
AB
AC
(IV)
A B#
A C#
(III)
A
(II)
A#
(I)
2

Fig.6.